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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/382,186	08/23/99	HANSEN	H [illegible]3733/0942

EXAMINER

HM12/0601

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ART UNIT	PAPER NUMBER
SAUNDERS, D	9

DATE MAILED: 06/01/01

s is a communication from the examiner in charge of your application.
MMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

sponsive to communication(s) filed on 2/26/01.

is action is **FINAL.**

ıce this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in cordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

ened statutory period for response to this action is set to expire 3 month(s), or thirty days, ver is longer, from the mailing date of this communication. Failure to respond within the period for response will cause plication to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR a).

sition of Claims

aim(s) 30-32 is/are pending in the application.
the above, claim(s) _____ is/are withdrawn from consideration.
aim(s) _____ is/are allowed.
aim(s) 30-32 is/are rejected.
aim(s) _____ is/are objected to.
aim(s) _____ are subject to restriction or election requirement.

:ation Papers

ee the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
ne drawing(s) filed on _____ is/are objected to by the Examiner.
ne proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
ne specification is objected to by the Examiner.
ne oath or declaration is objected to by the Examiner.

ty under 35 U.S.C. § 119

cknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

] received.
] received in Application No. (Series Code/Serial Number) _____.
] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

ertified copies not received: _____.

cknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

hment(s)

Notice of Reference Cited, PTO-892
nformation Disclosure Statement(s), PTO-1449, Paper No(s). 4, 5, 6
nterview Summary, PTO-413
Notice of Draftperson's Patent Drawing Review, PTO-948
Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

Applicant's election with traverse of Group II in Paper No. 8 (filed 2.26.01) is acknowledged, upon reconsideration the examiner has rejoined Groups II and III.

Claims 30-50 are pending and under examination.

The drawings are objected to because Figure 3 has left out the "l" of "light chain", recited to the left of construct A. Correction is required.

The disclosure is objected to because of the following informalities: the current status of various applicants referenced in the specification (e.g. pages 27, 28, 30) must be updated.

Appropriate correction is required.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

The sequences recited, for example at pages 13-14 and 40, have backbones with four or more amino acids which are not D-amino acids and, hence, fall within the scope of sequences encompassed by 37 CFR 1.821-1.825. Note also numerous sequences of four or more amino acids at pages 48-49.

Claims 32, 33 and 34 are objected to under 37 CFR 1.75 (I). Specifically, in claim 32, step (B); claim 33 step (2) (E), and claim 34 step (2) (E), two active verb steps of "growing" (or "combining") and "isolating" are recited in one paragraph. Note that 37 CFR 1.75 (I) requires each step of a claim to be separated by a line indentation. Applicant must either separate these steps or argue why they would both be inherently conducted is one step.

Claims 35-36 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The recitation of "monoclonal antibody" in claims 35-36 adds no limitation that is not inherent to base claim 30. Note that any antibody encoded by a DNA construct expressed by an expression cassette in a transformed host cell would inherently be "monoclonal", because such a host would not have been engineered to express any antibodies except for those encoded by the DNA construct.

Claims 30-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The conclusions of claims 30-31; claim 33, parts (1) (A) and (B) and (2) (A) and (B) and (2) (A) and (B) are indefinite. Note for example, in claim 30, the statement that the antibody or fragment is under the control of the regulatory regions is inaccurate. No protein, such as an antibody or fragment, is under the control of any such regulatory region. Rather it is the DNA

encoding the antibody or fragment that is under such control. Applicant could correct the conclusion of claim 30 by inserting --expression of-- between "wherein" and "said bispecific antibody". Claims 31, 33 and 34 can be analogously corrected by like insertions wherever such a concluding phrase regarding "control" occurs.

In claims 30, 31, 33 and 34 it is unclear what the "targetable conjugate" is in terms of what component is conjugated to what other component. It is suggested applicant define this conjugate as in original claim 1, part (C).

In claims 39-48, it is unclear, what portion of the conjugate of claim 1 the recited peptide, carbohydrate, hapten, or chelator constitutes. Are these entities, the carrier, the epitope, or the imaging/therapeutic agent of the conjugate?

Claims 39-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 39-42 contain new matter

Claims 39-42 were derived from original claims 14-17. The original claims recited the "conjugate comprises a peptide" etc. The new claims recite "the other arm specifically binds a peptide" etc. The new claims thus introduce a new concept of that component of the conjugate is bound by the "other arm". Please point out where this is supported in the specification.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same

invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 30-34 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 35-37 and 43-44 are of copending Application No. 09/337,756. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 35-50 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 35-37 and 43-44 of copending Application No. 09/337,756. Although the conflicting claims are not identical, they are not patentably distinct from each other because the natures of each of the arms of the encoded

bispecific antibody, as further defined in instant claims 35-50, are disclosed in the copending specification. Therefore copending claims 35-37 and 43-44 clearly encompass what is recited in instant claims 35-50.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 30-32, 35-36 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbet et al. (EP, 0,263,046) in view of Bosslet et al. (5,591,828).

Barbet et al. teach bispecific antibodies with a first arm directed to a target antigen on a cell and a second arm directed to a hapten component of a conjugate comprising one or more copies of the hapten and "effector" (i.e. a therapeutic or diagnostic agent) moieties. Barbet et al.

teach (page 5) production of such bispecific antibodies by chemically linking two monoclonal antibodies having the differing specificities, or by the quadroma technique. They do not teach a DNA construct which can encodes the bispecific antibody or a fragment thereof.

Bosslet et al. show that bispecific antibodies can be prepared by cotransfection of a host cell with a set of expression "cassettes" (i.e. plasmid), one of which encodes the light chains of the two antibodies and the other of which encodes the heavy chains of the two antibodies. It would have been obvious that the bispecific antibodies of Barbet et al. would be produced according to the co-transfected cell method of Bosslet et al. Note that Bosslet et al. teach their method as an alternative to or replacement for the chemical coupling and quadroma methods referenced at col. 1, lines 28-38.

In order to conduct the method of producing the bispecific antibodies of Barbet et al. according to the method of Bosslet et al. one would have been required to produce the above noted pair of expression cassettes or plasmids-- one for the H-chain fragment and one for the L-chain fragment. This pair is consistent with what is recited in instant claim 31. Either member of this pair is consistent with what is recited in claim 30. Note all elements for control of genetic expression are inherently present in any plasmid.

Claims 30-32, 35-36 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbet et al. in view of de Jonge et al. (Molec. Immunol.. 32, 1405, 1995).

The teachings of Barbet et al. with respect to bispecific antibodies having one arm directed to a target antigen and a second arm directed to a hapten moiety conjugated to a therapeutic agent have been noted supra.

De Jonge et al. teach production of bispecific antibodies having two arms, each comprised of an scFv fragment; these are expressed by a vector having all the elements of instant claim 30 (see Fig. 1.). It would have been obvious to prepare bispecific antibodies having the specificities taught by Barbet et al. by expressing the vectors of deJonge et al. Motivation to do so comes from the fact that deJonge et al. teach that their method of producing bispecific single chain antibody fragments has advantages, in terms of product isolation, in comparison to the quadroma production or chemical coupling methods taught by Barbet et al. See deJonge et al. at page 1405, col. 2 - page 1405, col. 1.

Claim 31 is included in the rejection, since deJonge et al. also show DNA constructs in vectors expressing the scFv fragment of each of the arms of the bispecific antibody. See Fig. 1.

Claims 30-32, 35-36 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin et al. (4,803,713) in view of Bosslet et al. or deJonge et al.

Goodwin et al. show a method involving administration of a "binding protein", followed by a "clearing agent", followed by an "epitopic compound". See col. 10 - col. 12, line 10, for example. The "epitopic compound" can include one or more hapten moieties, which are binding partners for an antibody, linked to an therapeutically active agent or imaging agent. See col. 4, line 55- col. 7, line 6. This "epitopic compound" corresponds to the targetable conjugate of the

instant claims. The "binding protein" can be comprised of monoclonal, bispecific antibodies, with one arm directed to a target tissue and the other arm directed to the epitopic compound. See col. 7, line 8 - col. 9, line 36, especially at col. 9, lines 3-36. This "binding protein" corresponds to the bispecific antibody of applicant's claims. Goodwin et al. teach production of their bispecific antibodies via the quadroma or via a chemical coupling method. Use of DNA constructs to produce bispecific antibodies, as taught by Bosslet et al. or de Jonge et al., in lieu of a quadroma or chemical coupling method, would have been obvious according to the rational set forth supra in the rejection based upon Barbet et al. as the primary reference.

Claims 30-33, 35-36, 41-43 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bardies et al. (J. Nucl. Med., 37,1853, 1996), or Gautherot et al. (J. Nucl. Med. 39, 1937, 1998).

Bardies et al. or Gautherot et al. show a bispecific monoclonal antibody with one arm directed to a target site and the other arm directed to In - DTPA. These are precisely the specificities shown by applicant in Examples 17 and 21 and employed 24. Also, note specification page 11 teaching that DTPA is a hapten component of a conjugate. The instant limitation that the other arm "binds a targetable conjugate" represents an intended use by applicant, and the binding of the prior art bispecific antibody to In -DPTA would inherently be directed to an In-DPTA hapten component of a targetable conjugate.

Bardies et al. and Gautherot et al. show a chemical coupling method for producing the bispecific antibody. Use of DNA constructs to produce bispecific antibodies as taught by Bosslet

et al. or de Jonge et al., in lieu of a chemical coupling method, would have been obvious, according to the rational set forth supra in the rejections based upon Barbet et al. as the primary reference.

Claims 30-32, 35-38, 41-43 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karacay et al. (Proceedings., 40, 644, 1999) or Karacay et al. (J. Nucl. Med. 40, no 5, suppl., p. 255, 1999) in view of Bosslet et al. or deJonge et al.

Karacay et al. teach a bispecific antibody having the specificities taught by Bardies et al. and Gautherot et al., both noted supra. Karacay et al. teach the further feature that the antibody of each arm is humanized, in accord with the limitations of instant claims 37-38. The bispecific antibody of Karacay et al. is produced by chemical conjugation. Obviousness of producing this antibody by expressing DNA constructs encoding a bispecific antibody according to the teachings of Bosslet et al. or deJonge et al. follows the same rational set forth supra using Bardies et al. or Gautherot et al. as primary references.

The examiner notes that the above cited references of Bardies et al., Gautherot et al. and Karacay et al. (Proceedings ... and J. Nucl. Med.) use a bispecific antibody with one arm directed to the In-chelator. Applicant appears to teach away from this in the paragraph spanning specification pages 12-13, but then uses a bispecific antibody with the same specificities as the antibodies of the prior art in specification Example 24. Thus the examiner considers it proper to have cited these references. Clarification as to the nature of the invention is requested.

Claims 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbet et al., Goodwin et al., Bardies et al., or Gautherot et al., any in view of Bosslet et al. or de Jonge et al. as applied to claims 30 and 31 above, and further in view of Goldenberg (WO 96/04313).

Each of the primary references, teaching murine bispecific antibodies, has been cited, in combination with either of the secondary references, against claims 30 and 31 in further above stated rejections. Goldenberg teaches (pages 6, 18 and 21) that use of humanized antibodies is known for the targetting of therapeutic or imaging agents. It would have been obvious to provide DNA constructs encoding humanized bispecific antibodies, having the specificities of the primary references, since Goldenberg teaches that use of humanized antibodies avoids problems associated with the immunogenicity of murine antibodies.

Any inquiry concerning this communication should be directed to David Saunders at telephone number (703) 308-3976.

David A. Saunders

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D. Saunders:jmr

May 9, 2001

May 24, 2001